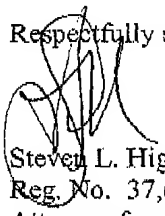
REMARKS

Pursuant to discussions with Examiner Zitomer, held on July 11 and 14, 2003, applicants now provide the preceding amendments with the understanding that these will place the application in condition for allowance. Should Examiner Zitomer have any questions regarding these amendments, a telephone call to the undersigned is invited.

Respectfully submitted,



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APPENDIX A1: MARKED UP COPY OF CLAIMS

1. (Twice amended) A method for [assessing] determining proper folding and/or solubility of a protein of interest comprising:

a) providing an expression construct comprising (i) a gene encoding a first polypeptide comprising said protein of interest fused to a first segment of a marker protein, [wherein said first marker segment has only systematic effects on the folding or solubility of the protein of interest,] and (ii) a promoter active in a selected host cell and operably linked to said gene;

b) expressing said first polypeptide in said host cell that also expresses [a second polypeptide consisting essentially of] a second segment of said marker protein, wherein said second marker segment combines with said first marker segment to form a functional marker protein when said first polypeptide is properly folded; and

c) [assessing the ability of said first and second marker segments to combine to form a functional] measuring marker protein function,

wherein a greater degree of marker protein function, as compared to marker protein function observed with appropriate negative controls, indicates [improved] proper folding and/or solubility of said protein of interest.

4. (Amended) The method of claim 1, wherein said marker protein is selected from the group consisting of a [target binding] protein that binds said protein of interest, an enzyme, a protein inhibitor, a fluorophore and a chromophore.

5. (Amended) The method of claim 4, wherein said marker protein is a [target binding] protein that binds said protein of interest.

21. (Amended) The method of claim 20, wherein said nematode cell is a [*C.*] *Caenorhabditis elegans* cell.

23. (Amended) The method of claim 22, wherein said host cell is a [*S. fugeria*] *Spodoptera frugiperda* cell.

30-40. (Canceled).

APPENDIX A2: MARKED UP COPY OF SPECIFICATION

Page 65, lines 1-6:

G32D/I33P -

5′-GATGCTCAACGGTGACTTTAGGATCGGTATCTTCTCGAATTTC-3′ (SEQ ID NO: 1)

G32D -

5′-CAACGGTGACTTTAATATCGGTATCTTTCTCG-3′ (SEQ ID NO:2)

133P -

5′-GGTGACTTTAGGTCCGGTATCTTTCTCG-3′ (SEQ ID NO:3)

APPENDIX B: CLEAN COPY OF PENDING CLAIMS (UNOFFICIAL)

1. A method for determining proper folding and/or solubility of a protein of interest comprising:

   a) providing an expression construct comprising (i) a gene encoding a first polypeptide comprising said protein of interest fused to a first segment of a marker protein, and (ii) a promoter active in a selected host cell and operably linked to said gene;
   b) expressing said first polypeptide in said host cell that also expresses a second segment of said marker protein, wherein said second marker segment combines with said first marker segment to form a functional marker protein when said first polypeptide is properly folded; and
   c) measuring marker protein function,

   wherein a greater degree of marker protein function, as compared to marker protein function observed with appropriate negative controls, indicates proper folding and/or solubility of said protein of interest.

2. The method of claim 1, wherein said first polypeptide comprises said first marker segment fused C-terminal to said protein of interest.

3. The method of claim 1, wherein said first polypeptide comprises said first marker segment fused N-terminal to said protein of interest.

4. The method of claim 1, wherein said marker protein is selected from the group consisting of a protein that binds said protein of interest, an enzyme, a protein inhibitor, a fluorophore and a chromophore.

5. The method of claim 4, wherein said marker protein is a protein that binds said protein of interest.

6. The method of claim 5, wherein said target binding protein is ubiquitin.

7. The method of claim 4, wherein said marker protein is a chromophore.

8. The method of claim 7, wherein said chromophore is green fluorescent protein, blue fluorescent protein, yellow fluorescent protein, luciferase or aquorin.

9. The method of claim 4, wherein said marker protein is an enzyme.

10. The method of claim 9, wherein said enzyme is β-galactosidase, cytochrome c, chymotrypsin inhibitor, Rnase, phosphoglycerate kinase, invertase, staphylococcal nuclease, thioredoxin C, lactose permease, amino acyl tRNA synthase, and dihydrofolate reductase.

11. The method of claim 10, wherein said enzyme is β-galactosidase.

12. The method of claim 11, wherein said first marker segment is the α-peptide of β-galactosidase, and said second segment is the ω-peptide of β-galactosidase.

13. The method of claim 1, wherein said protein of interest is Alzheimer's amyloid peptide (Aβ), SOD1, presenillin 1 and 2, α-synuclein, amyloid A, amyloid P, CFTR, transthyretin, amylin, lysozyme, gelsolin, p53, rhodopsin, insulin, insulin receptor, fibrillin, α-ketoacid dehydrogenase, collagen, keratin, PRNP, immunoglobulin light chain, atrial natriuretic peptide, seminal vesicle exocrine protein, β2-microglobulin, PrP, precalcitonin, ataxin 1, ataxin 2, ataxin 3, ataxin 6, ataxin 7, huntingtin, androgen receptor, CREB-binding protein, dentaorubral pallidoluysian atrophy-associated protein, maltose-binding protein, ABC transporter, glutathione S transferase, and thioredoxin.

14. The method of claim 1, wherein a gene encoding said second polypeptide is carried on a chromosome of said host cell.

15. The method of claim 1, wherein a gene encoding said second polypeptide is carried episomally in said host cell.

16. The method of claim 1, wherein said host cell is selected from the group consisting of a bacterial cell, an insect cell, a yeast cell, a nematode cell, and a mammalian cell.

17. The method of claim 16, wherein said host cell is a bacterial cell.

18. The method of claim 17, wherein said bacterial cell is *E. coli*.

19. The method of claim 18, wherein said promoter is the *Taq* promoter; T7 promoter, or the P_{lac} promoter.

20. The method of claim 16, wherein said host cell is a nematode cell.

21. The method of claim 20, wherein said nematode cell is a *Caenorhabditis elegans* cell.

22. The method of claim 16, wherein said host cell is an insect cell.

23. The method of claim 22, wherein said host cell is a *Spodoptera frugiperda* cell.

24. The method of claim 16, wherein said host cell is a yeast cell.

25. The method of claim 14, wherein said promoter is CupADH or Gal.

26. The method of claim 16, wherein said host cell is a mammalian cell.

27. The method of claim 26, wherein said promoter is PepCk or tk.

28. The method of claim 1, wherein said negative control utilizes a host cell lacking the second polypeptide.

29. The method of claim 1, wherein said negative control utilizes a fusion protein that is improperly folded and/or insoluble.